HuGE Fact Sheet

HLA-DPB1 *E69 and Chronic Beryllium Disease

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Gene

HLA-DPB1 is located on chromosome 6p12.3 and codes for Human Leukocyte Antigen, a Major Histocompatibility Class II (MHCII) molecule. MHCII molecules are heterodimeric, having a and ß chains, *DPB1* codes for the ß chain. These molecules are responsible for initiation of the immune response through antigen presentation to T cells.

Prevalence of Gene Variants

There are 103 known variants of *HLA-DPB1* (Table 1). The supratypic marker *HLA-DPB1*^{*E69}, coding for glutamic acid at the 69th residue of the mature protein, is found in 34 of those variants. The allelic frequency of the supratypic marker *HLA-DPB1*^{*E69} is highly variable occuring in: <1% of some Amerindian tribes, 20-25% of Caucasian-Americans and African-Americans, >40% of Chinese. In Asia-Oceana it varies between <1% and >55%. Frequencies are typically based on studies of 20-150 individuals (1).

Disease Burden

Chronic Beryllium Disease (CBD) is caused by exposure to beryllium (Be), in the form of particles of BeO, BeF, other Be-salts, Be-metal, or Be-alloy. It has been estimated that approximately 1-12% of workers in the primary industry are immunologically sensitized to beryllium. Of those, 36-100% develop CBD (2). There is evidence that certain tasks, such as machining which has a relatively high exposure, pose greatest risk of CBD (3). Data from 5 molecular epidemiological case-control studies have shown odds ratios for CBD among *HLA-DPB1*^{*E69} positive beryllium-workers to be between 4 and 80. Studies in general were hampered by small numbers (6-33 cases, 44-121 controls). Genotyping used several different methods, from oligonucleotide hybridization to high resolution DNA sequencing.

Interactions

Attempts to estimate gene-gene and gene-environment interactions have relied on too few study subjects. However, there is a suggestion that there are interactions of *HLA-DPB1*^{*E69} with: *HLA-DPB1*^{*R74}, *TNF-a-308*2*, and high exposure tasks in the beryllium industry (4, 5).

Laboratory Tests

Identification of *HLA-DPB1*^{*E69} is facile and can be accomplished by reliable molecular methods, such as RFLP (6). However, because of the relatively high carrier frequency of this supratypic marker among Caucasian-Americans and African-Americans (30-40%) compared with the relatively low CBD prevalence among US beryllium-workers (1-5%), its positive predictive value (PPV) is probably too low to have a significant impact on CBD burden through genetic testing. Although the data required to calculate a true PPV for this marker do not yet exist, we have estimated the PPV to be between 7 and 14% (6).

Population Testing

The positive public health impact of genetic research on *HLA-DPB1* and CBD will be accomplished, not through genetic testing, but rather the development of better research tools (animals genetically modified with human genes), development of post-exposure interventions,

and development of an exposure limit that protects all workers irrespective of their genotype (6). We are aware that a major U.S. beryllium manufacturing company has conducted a limited pilot project in which applicants for employment were offered the opportunity for anonymous genetic testing through an independent academic center. To better understand the ethical and legal issues surrounding workplace genetic testing, the company has discussed this pilot project in several conference settings. The ethical issues concerning genetic information in relation to employment requires that beryllium workers be educated about the risks and benefits associated with obtaining genetic test results.

References

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6. Weston A, Ensey J, Kreiss K, et al. Racial differences in prevalence of a supratypic HLA-genetic marker immaterial to pre-employment testing for chronic beryllium disease. *Am. J. Ind. Med.* 41:457-465, 2002.

Web Sites

1. European Bioinformatics Institute IMGT/HLA Database
2. Beryllium Support Group

Table 1: List of Known *HLA-DPB1* Alleles, as of January 17, 2003[1, 2]

DPB1*010101	DPB1*1501‡	DPB1*3401	DPB1*5701	DPB1*7801
DPB1*010102	DPB1*1601 †	DPB1*3501	DPB1*5801 †	DPB1*7901
DPB1*010102 †	DPB1*1701 †	DPB1*3601	DPB1*5901	DPB1*8001
DPB1*020103 †	DPB1*1801	DPB1*3701 †	DPB1*6001	DPB1*8101 †
DPB1*020104 †	DPB1*1901 †	DPB1*3801	DPB1*6101 N	DPB1*8201
DPB1*020105 †	DPB1*200101	DPB1*3901	DPB1*6201	DPB1*8301
DPB1*020106 †	DPB1*200102	DPB1*4001	DPB1*6301	DPB1*8401
DPB1*0202 †	DPB1*2101 †	DPB1*4101 †	DPB1*6401N †	DPB1*8501
DPB1*030101	DPB1*2201 †	DPB1*4401 †	DPB1*6501	DPB1*8601 †
DPB1*030102	DPB1*2301	DPB1*4501	DPB1*6601	DPB1*8701
DPB1*0401	DPB1*2401	DPB1*4601 †	DPB1*6701	DPB1*8801 †
DPB1*0402	DPB1*2501	DPB1*4701 †	DPB1*6801	DPB1*8901
DPB1*0501	DPB1*260101	DPB1*4801 †	DPB1*6901	DPB1*9001

DPB1*0601 †	DPB1*260102	DPB1*4901	DPB1*7001	DPB1*9101
DPB1*0801 †	DPB1*2701	DPB1*5001	DPB1*7101 ‡	DPB1*9301
DPB1*0901 †	DPB1*2801	DPB1*5101	DPB1*7201	DPB1*9301 †
DPB1*1001 †	DPB1*2901 †	DPB1*5201	DPB1*7301	DPB1*9401[3]
DPB1*110101‡	DPB1*3001 †	DPB1*5301	DPB1*7401†	DPB1*9501[3]
DPB1*110102‡	DPB1*3101	DPB1*5401 †	DPB1*7501	DPB1*9601
DPB1*1301 †	DPB1*3201 †	DPB1*5501 †	DPB1*7601	
DPB1*1401	DPB1*3301 †	DPB1*5601	DPB1*7701	

1. Information taken from http://www.ebi.ac.uk/imgt/hla/allele
2. Codon 69 coding for a glutamic acid at residue 69 of the mature protein is most strongly associated with berylliosis. Sixty-two alleles code for lysine (K) at this position, †34 code for glutamic acid (E), and † 5 code for arginine (R).
3. The identity of two alleles remains confidential. Nomenclature rules for HLA genes were modified in November 2002, Table 1 reflects those changes.